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How are calcimimetics influencing our management of uraemic hyperparathyroidism?

Simon J. Steddon[1], John Cunningham[2]

[1] Department of Renal Medicine and Transplantation, Bart's and the London NHS Trust, Whitechapel, London E1 1BB, United Kingdom.
[2] The Centre for Nephrology, The Royal Free and University College Medical School, London NW3, United Kingdom

INTRODUCTION

Renal osteodystrophy is a heterogeneous disorder leading to diminished bone strength in patients with impaired kidney function. Although virtually ubiquitous beyond chronic kidney disease (CKD) stage 3, its clinical management remains a formidable challenge. Much attention has focused on the prevention and treatment of secondary hyperparathyroidism (SHPT). In this scenario, hypocalcaemia, hyperphosphataemia and impaired renal 1,25-dihydroxyvitamin D production all contribute to excess PTH secretion and accordingly constitute the principal targets for therapeutic intervention. Although very effective, treatment with vitamin D sterols and phosphate binders is frequently complicated by oversuppression of bone turnover, hypercalcaemia, hyperphosphataemia and extra-skeletal calcification. Far from simple therapeutic inconveniences, these are thought to contribute significantly to the burden of cardiovascular disease in CKD patients and have provided the major impetus behind the development of increasingly refined therapeutic targets, the achievement of which, it is hoped, will eventually translate into substantial improvement in clinical outcomes. These revised objectives have also set the scene for a new generation of treatments, including novel phosphate binders, structurally modified vitamin D analogues and, recently, the calcimimetic agents, with the intention of helping clinicians meet the amended goals without significant hazards for their patients.

THE CALCIUM SENSING RECEPTOR

Cloned in 1993, the calcium sensing receptor (CaR) comprises a large extracellular region, seven transmembrane domains and an intracellular tail[1]. Signalling involves coupling through G_i proteins to adenylate cyclase and G_q/G_{11} proteins to phospholipase C (figure 1). The receptor is constitutively expressed across multiple cell types and is increasingly credited with roles in several diverse aspects of cellular function (table 1)[2]. Its chief purpose, however, is the control of extracellular calcium concentration and thereby the regulation of steady state parathyroid hormone (PTH) secretion.

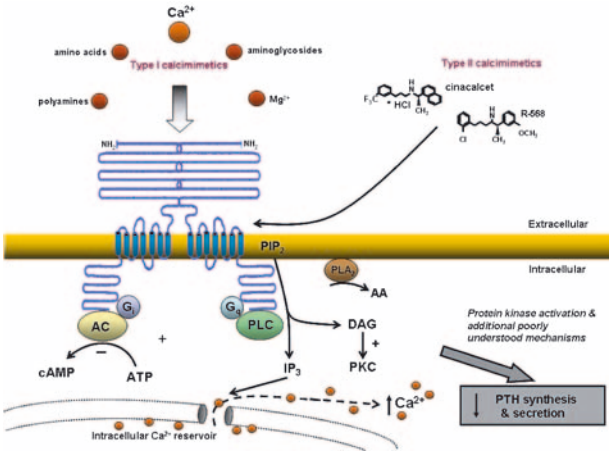

Figure 1. The CaR is a dimeric structure with an extremely large extracellular domain, seven transmembrane domains and an intracellular tail. Intracellular signal transduction is complex, with several pathways implicated, and many of the downstream events remain unclear. In overview, G_q protein mediated interaction with phospholipase C (PLC) results in hydrolysis of phosphatidylinositol bisphosphate (PIP_2) to form inositol triphosphate (IP_3) and diacylglycerol (DAG). IP_3 acts to increase Ca^{2+} release from intracellular stores, while DAG activates protein kinase C (PKC). In addition, G_i protein mediated interaction with adenylate cyclase (AC) leads to reductions in cellular cAMP, while phospholipase A_2 (PLA_2) activation leads to arachidonic acid (AA) release.

THE CALCIUM SENSING RECEPTOR AND SECONDARY HYPERPARATHYROIDISM

A central component of the pathogenesis of SHPT in CKD is rightward shift of the sigmoidal curve describing the relationship between PTH and ambient calcium concentration in the parathyroid glands[3]. Pathologically, this right shift probably results from progressive under-expression of parathyroid CaR. With parallel reductions in vitamin D receptor (VDR) expression, suppression of hyperparathyroidism requires inordinately high ambient calcium and calcitriol concentrations, both of which are not without serious risk. The practical result is that conventional SHPT treatment with phosphate binders and vitamin D metabolites often places the patient on the threshold of, or overtly within, the realms of calcium and phosphorous toxicity. Such poor control of uraemic mineral metabolism is clearly associated with cardiovascular morbidity and mortality. In a study of 12833 haemodialysis patients, raised levels of phosphorus (P<0.01) and calcium phosphorus product (CaxP) (P<0.005) were associated with an increased risk of death[4]. Moreover, in a study that included almost 6500 haemodialysis patients, increasing severity of hyperphosphataemia was unequivocally associated with increasing mortality[5]. The perfect treatment of SHPT would secure optimal serum PTH concentrations, prevent parathyroid gland hyperplasia while maintaining normal physiological circulating concentrations of calcium and phosphorus. It would also prevent soft tissue calcification and maintain normal bone turnover. Although both parathyroid cell proliferation and secretion of PTH are influenced by serum calcitriol and phosphorus concentration, CaR activation by calcium typically overrides their stimulus, making it an extremely appealing therapeutic target.

Table 1. CaR tissue distribution and putative function. In many cases function remains speculative or is implied from the observed effects of a change in ambient Ca^{2+} concentration within a particular cellular/tissue environment. Data from both *in vitro* and *in vivo* models. For a comprehensive review, see reference 2.

Tissue	Region/Cell type	Confirmed or *putative function
Parathyroid glands	Chief cells	Regulation of PTH gene expression, PTH secretion and parathyroid gland hyperplasia
Kidney	Proximal tubule	*Regulation of transporter function (e.g. Na^+-K^+-ATPase)
	Thick ascending limb	Control of urinary Ca^{2+} excretion
	Distal nephron	Urinary concentration Ca^{2+} reabsorption
Thyroid	C cells	Activation leads to calcitonin release.
Skeleton	Osteoclasts	*Osteoclastogenesis *Bone resorption
	Osteoblast	Proliferation, via activation of the Jun-terminal kinase pathway and upregulation of mitogenic gene expression
	Chondrocytes	*Regulation of gene expression (e.g. proteoglycans)
G.I. tract	Gastric surface epithelial cells Gastrin secreting cells	*Proliferation *Gastrin release
	Proximal small intestine	*Epithelial proliferation and differentiation *Motility *Influences secretory/absorptive function
	Colonic epithelium	*Epithelial cell differentiation *Absorption/secretion of Ca^{2+} *Fluid transport (?therapeutic target in secretory diarrhoea)
Placenta	Villous and extravillous regions	*Transplacental Ca^{2+} transport
Nervous system	Neurones (hippocampus and cerebellum), oligodendrocytes and astrocytes	*Regulation of ion channel activity *Neuronal excitability *Myelin formation
Bone marrow	Megakaryocytes, erythroid precursors and others (also myeloma cells)	Unknown. Also expressed on platelets and monocytes in peripheral blood.
Pituitary	Anterior pituitary	*Regulation of growth hormone and prolactin secretion
Skin	Keratinocytes	*Differentiation
Eye	Lens epithelium	*Maintenance of structural integrity
Breast	Ductal tissue	*Ca^{2+} transport into milk. Possibly involved in the propensity of breast cancer cells to metastasise to bone.
Pancreas	Endocrine (islet cells)	Unknown
	Exocrine (ductal cells)	*Control of Ca^{2+} content of pancreatic secretions

CALCIMIMETIC AGENTS

Calcimimetic agents are small molecules that bind to the CaR and mimic the effect of an elevated extracellular calcium concentration. Type I calcimimetics, which include calcium itself and several other cationic compounds, directly activate the CaR. Type II agents are not strictly agonists of the receptor, rather positive allosteric modulators able to bind within the transmembrane region and increase sensitivity to ambient calcium (table 2)[6]. The functional consequence of this is a substantial leftward shift of the parathyroid calcium relationship in a manner that very satisfactorily reverses the dysregulation characteristic of uraemia. As could be predicted, calcimimetics reduce PTH release whilst simultaneously diminishing serum calcium concentration in CKD patients. Of particular interest are the parallel reductions in serum phosphorous, presumably reflecting reduced efflux from bone. Typical reductions are in the order of 30 to 50% for PTH and 5 to10% for serum calcium, phosphate and the CaxP product. In this respect calcimimetic agents differ importantly from currently available phosphate binders and vitamin D compounds (table 3). Initial studies with the prototype calcimimetic agent, NPS R-568, were extremely encouraging, demonstrating dose-dependent suppression of PTH and calcium. In models of uraemic SHPT it reduced parathyroid cell proliferation and progressive glandular hyperplasia[7], while improving bone turnover[8]. Marked interindividual variation in pharmacokinetics led to the withdrawal of NPS R-568 in favour of cinacalcet, a compound enjoying a more predictable duration of action. An extensive clinical programme conducted with this agent over the last few years has shown it to be generally well tolerated, with upper GI intolerance the only side effect occurring with significant frequency. These are experienced by about 10 to 15% of patients, although rarely with sufficient severity to require cessation of therapy. Despite the ubiquitous distribution of the calcium receptor, CNS, cardiac and other side effects have not been noted. Mild hypocalcaemia is a frequent and predictable consequence of treatment which, though rarely problematic, may require dose reduction on occasion.

Table 2. Agonists and allosteric modulators of the CaR

Type I calcimimetics (agonists)	**Type II calcimimetics (allosteric modulators)**
Divalent and trivalent inorganic cations	**Phenylalkamines**
Calcium, Magnesium, Lanthanum, Gadolinium, Barium, Cadmium, Cobalt, Nickel, Iron (Fe^{2+}), Lead, Aluminium	***First generation***
	NPS R-467 NPS R-568
Polyamines	***Second generation***
Spermine Spermidine Putrescine	Cinacalcet (AMG 073/KRN1493)
Aminoglycoside antibiotics	
Streptomycin Gentamicin Neomycin Tobramycin G418	
Polyvalent amino acids and peptides	
Polylysine Polyarginine Amyloid ß peptide	

Table 3. Actions of current treatments on calcium, phosphorus, CaxP and PTH concentrations. Arrows depict direction of travel.

	Calcium-based binder	Calcium-free binder	Vitamin D sterols	Calcimimetic
PTH	↓↓	↓	↓↓↓	↓↓↓
Calcium	↑↑	↔ or ↑	↑	↓
Phosphorus	↓↓	↓↓	↑	↓
CaxP	↓	↓	↑	↓

CLINICAL STUDIES WITH CALCIMIMETICS

The evidence for the clinical efficacy of cinacalcet has burgeoned rapidly. An 18-week dose-titration trial in 71 haemodialysis patients with uncontrolled SHPT receiving standard treatment with vitamin D metabolites and phosphate binders showed a 33% vs. 3% reduction in PTH in cinacalcet and placebo arms respectively. CaxP rose by more than 11% in the placebo group, but fell by almost 8% with the calcimimetic[9]. The largest study to date combined European and North American experience to show a 30% reduction in PTH from baseline values in two-thirds of patients, compared to 11% in those receiving standard care. CaxP was unchanged in the conventional group, but fell 15% in the cinacalcet arm[10]. More recent studies suggest that the biochemical benefits of treatment are sustained into the medium and long term[11] and may be applicable to other CKD scenarios besides haemodialysis, including pre-dialysis[12], peritoneal dialysis[13] and persistent post-transplant hyperparathyroidism[14,15]. It is also apparent that an additional consequence of calcimimetic treatment is much higher compliance with K/DOQI and other national targets[16].

CLINICAL OUTCOMES AND POTENTIAL ROLE FOR CALCIMIMETICS

While there is little doubt that treatment with cinacalcet is well tolerated and, biochemically at least, extremely effective, it should also be appreciated that it is extremely expensive, such that uptake in many countries may be limited or non-existent. Consequently, an important outstanding issue is how best to decide where need is greatest. In order to determine this, we need to gather more data regarding clinical outcomes and to undertake a rational approach to patient selection. Recent retrospective analysis of prospectively gathered data from the phase 3 programme has yielded potentially important information in this regard. Predictably, the parathyroidectomy rate was much lower than that in conventionally treated patients, as was fracture rate. While no differences in all cause or cardiovascular mortality were seen, the frequency of hospital admission for cardiovascular disease was lower in cinacalcet treated patients. In addition, a panel of quality of life measures showed a collective enhancement amongst those receiving the calcimimetic[17]. This suggests that there may be a real clinical, not just biochemical, gain for patients treated with cinacalcet. It is too early to know whether these clinical benefits are limited to particular patient subgroups. From the biochemical standpoint, however, it makes sense to choose therapy (vitamin D sterol or calcimimetic) according to the phenotype of the patient (table 4). The so called 'vitamin D phenotype' is the patient with SHPT in whom serum calcium, phosphate and CaxP product are all in the lower part of the normal range or even subnormal. In this type of patient vitamin D therapy is usually effective in bringing biochemical parameters to target. The risk of hypercalcaemia or hyperphosphataemia is relatively low in this situation.

Table 4. The two phenotypes frequently encountered in CKD patients with hyperparathyroidism

	Parathyroid function	Calcium	Phosphorus	CaxP Product
'Vitamin D phenotype'	Appropriate	Low-normal or low	In target	In target
'Calcimimetic phenotype'	Dysregulated; impaired calcium sensing	High normal or high	Above target	High

The designated 'calcimimetic phenotype' is potentially more difficult to treat. Here the hyperparathyroidism is accompanied by a high normal or frankly elevated serum calcium, often with elevation of serum phosphate and CaxP product. Treatment with vitamin D sterols, while effectively reducing PTH, inevitably aggravates the hypercalcaemia and hyperphosphataemia. This type of patient stands to benefit more from calcimimetic therapy. Predictably enough, vitamin D ligands and calcimimetics work well in tandem. Their modes of action at the level of the parathyroid cell are different and effects on PTH appear to be additive. In addition, experience in clinical practice suggests that the use of very small doses of a cinacalcet frequently modifies the substrate in a manner such as to make the use of vitamin D sterols easier. As experience grows with the calcimimetic agents, so also will our ability to use vitamin D metabolites and cinacalcet in the most effective complementary manner.

CONCLUSION

If used in rational combination with conventional therapies in appropriately selected patients, the calcimimetic agents are likely to provide welcome assistance in achieving the more rigorous targets recently developed for PTH, calcium and phosphorus in the context of CKD. Though more evidence regarding genuine clinical, as opposed to just biochemical, benefit is mandatory, the calcimimetics show great promise for the prevention of bone pathology, as well as encouraging early signs of useful impact on cardiovascular events and subjective well-being in patients with impaired kidney function.

Corresponding author:
Professor John Cunningham
The Centre for Nephrology
The Royal Free and University College Medical School
Rowland Hill St
London NW3
United Kingdom
drjohncunningham@aol.com

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